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Inheritance and Environment in Affective Psychoses

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Introduction

The concept of heredity took on a new significance for psychiatry in the middle of the 19th century when Darwin (1859, 1964) launched his Theory of Evolution onto an unsuspecting world. It was Kraepelin (1913), in particular, who recognised its consequences and took steps to apply it in "Das manisch-depressive Irresein", pointing out the familial hereditary aspects so typical of this disease.

The idea of illness-units, which Kraepelin again used in practice (1887), grew in popularity at the beginning of this century under the term *nosology*. Illness, it appeared, had an etiological basis, the condition itself was described in detail and its likely progress and prognosis could be predicted.

In 1971, Kuilman published an erudite and exhaustive analysis of the endogenic concept. Following in Moebius's footsteps, he pinpointed the relationship between heredity, degeneration and endogeny ("endogenie") and made a distinction between the hereditary traits (endogeny) and the genetic transmissibility (degeneration). And anticipating what was to come, Kuilman predicted that the concept of degeneration would, after a period of quiet "retirement", make a world come-back to the clinical language, this time as an atypical variant of the manic-depressive psychosis.

One meets only very occasionally in the current literature adjectives like "endogenous" and then only in terms such as "endogenous depression", which one might put on the same par as "vital depression" (Van Praag 1977) and "major depression with melancholia" (DSM-III 1980; DSM-III-R, 1987). In this paper, we have used the term "affective psychosis" as a synonym for "affective disorder" and "depression/mania".

Syndromal classification

The introduction of biological psychiatry and psycho-pharmacology brought about a number of changes in the classical psychiatric nosology with regard to descriptions of symptoms and specification of terms such as: course, pathogenesis and etiology (Van Praag & Leynse 1965). *Pathogenesis* was defined as "the constellation of causal dysfunctions which enable disorders to occur" and *etiology* as "all factors – hereditary, acquired, somatic, psychological and social – which have contributed to the occurrence of the cerebral dysfunctions" (Van Praag 1977). It has been accepted that there are, in general, two types of depression: vital (major depression, with melancholia, DSM-III, 1980) and personal (dysthymic disorder, DSM-III, 1980). Mixed forms of both types are, of course, also quite common.

Although this typology of depression should be understood as non-specific in the etiological sense, the DSM-III (1980) and DSM-III-R (1987) which are also based

on this kind of non-specificity, are not completely devoid of the essential dichotomy philosophy of a nosological representative such as Kraepelin (Katschnig et al. 1986).

We have the impression, therefore, that psychiatric behaviour, be it depressive, manic or a mixed form of both, develops as a result of a composition of several elements, biological (and genetical), psychosocial and somatological. The concept of the interaction between these factors will be outlined latter on.

Biological factors

Research has shown that deep cerebral systems (of alerting, orientating, motivational and behavioural nature) utilize the biogenic amines as neurotransmitters (Whybrow et al. 1984). It has been shown that increases in amines (such as catecholamines [CA] like dopamine [DA] and norepinephine [NE], and serotonin [5-HT]) might be associated with hypomania or mania, whereas decrements in these amines could be associated with depression (Jacobsen 1964). The theory that several different biochemical functional disorders underlie psychiatric syndromes and that each of these disorders is responsible for certain features of the syndrome (Van Praag & Leynse 1965), is called *functional pathology hypothesis*. This hypothesis is congruent with the so-called biochemical heterogeneity of affective disorders (i.e. depression and mania) and has been substantiated by several research workers (e.g., Van Praag 1974, Maas 1983). Noradrenergic dysregulation, for instance, could account, in part, for inappropriate activation of stress response system (e.g., excess cortisol levels with loss of normal diurnal variation and resistance to suppression), typical for even the most withdrawn depressive disorders.

Cerebrospinal fluid (CSF) and urine metabolite studies suggest that activity of 5-HT in the brain may be more consistently decreased, perhaps accounting for sleep and appetite disturbances and for the reduced capacity for self-soothing of the depressed patient. Acethylcholine (AC), a transmitter in punishment and withdrawal circuit, has been thought to be hyperactive in depression. DA, which along with AC is important in motor and motivational systems, may also be implicated in depression.

The biogenic amine hypothesis of depression (stating that the biological basis of endogenous depression is a lack of adequate levels of amine transmitters such as NE and 5-HT at the synaptic level), has been amended in recent years by the introduction of sophisticated receptor research techniques, such as radioligand binding and microiontophoresis (Aston-Jones et al. 1984, Siever & Davis 1985, Heninger et al. 1988).

The application of these techniques has led to the following results: the supersensitivity of the beta-receptors in depression is a compensatory response to the NE deficiency that brings about a hyperfunctioning of the neuronal system. The depressive symptoms are ameliorated via the antidepressants because of the possible down-regulation of the post-synaptic neuronal response and the alpha-2-receptors. Such a down-regulation increases the amount of NE released, thereby overcoming the deficiency that exists in depression (Heninger & Charney 1987).

It should also be borne in mind that the action mechanism of most, if not all, antidepressant treatments is the reduction in number of both the beta-adrenergic and the 5-HT-2-serotonergic receptors following chronic or semi-chronic anti-depressant administration. Such an obvious common factor of this kind may point toward a shared site of action and, as such, toward an underlying pathophysiology of depression involving both the adrenergic and the serotonergic neurotransmitter systems (Cooper et al. 1986, Heninger & Charney 1987). Depression is associated with the disruption of important biological activity

rhythms. The sleep cycle may be phase advanced (turned ahead), first producing early onset of sleep and then of awakening with respect to the time of day (Wehr & Goodwin 1983). A number of studies have also demonstrated changes in cellular immunity in depressed patients (Kronfol et al. 1983, Schleifer et al. 1984, Calabrese et al. 1986).

Genetical Factors

A major difficulty is the variation in diagnostic criteria, used in the various studies. In kinship studies, Perris (1966) for instance, required at least three episodes of depression before applying the diagnosis of unipolar depression, whereas other studies required only one such period. Some investigators use hypomania in identifying bipolar cases (the so-called bipolar II) whilst others do not. When probands are studied in a clinical setting, it is necessary to consider their comparability with cases in the community (Wing & Bebbington 1982). Several studies have subtyped probands and blood relatives according to Leonard's (1959) bipolar-unipolar distinction. It is generally accepted that affective disorders are familial (see Angst 1966, Perris 1966, Mendlewicz & Rainer 1974, Winokur et al. 1982). The rate of bipolar illness is the highest in relatives of bipolar probands, intermediate in relatives of unipolar probands and lowest in relatives of non-affected persons. Estimations of the occurrence of bipolar illness in various populations, have been reasonably consistent, in contrast to similar investigations of unipolar illness, which have been rather more variable.

Akiskal et al. (1977) found that even some (mild) unipolars will become bipolar. Before looking at the relationship between bipolar and unipolar illness, it is necessary to verify the precise diagnostic criteria used for case definition. A lack of clarity in this matter often causes a number of methodological problems when studying comparisons of bipolar and unipolar probands.

Unipolar illness is usually reported to be more common in women than in men, whereas bipolar illness has been found to occur to approximately the same degree in both sexes. Bipolar illness has been found to have an earlier onset age than unipolar illness and an earlier onset in a proband of either type tends to be associated with a higher morbidity rate in relatives.

The hypothesis that the origin of affective psychosis does have a genetic component is supported by twin studies. Most of these studies found a much greater likelihood of psychosis in monozygotic (MZ) pairs than in dizygotic (DZ) pairs (Rosanoff et al. 1953, Allen et al. 1976, Bertelsen et al. 1977).

MZ twins who were studied as having a high degree of environmental sharing do not, on average, show any greater similarity for traits such as personality or IQ, than MZ twins with a less marked degree of environmental sharing (Loehlin & Nicholas 1976). In their adoption study, Mendlewicz & Rainer (1977) found support for the genetic hypothesis for bipolar illness. The increased rates of unipolar illness in the bioological parents of both bipolar groups, also supports the hypothesis that unipolar illness is, to some extent at least, transmitted by a common genetic factor within these families. Cadoret's study (1978) also leans towards a genetic hypothesis in affective psychoses, whereas Von Knorring et al.'s (1983) data do not. These studies were, however, methodologically very different and therefore do not lend themselves readily to comparison. Notwithstanding the fact that familial factors in the etiology of affective psychoses have been ascertained, no single mode of inheritance has been unequivocally established. Some of the reasons are unresolved clinical diagnostic problems, phenotypic heterogeneity and methodological issues.

Winokur et al. (1969) studied 62 bipolar probands and suggested an X-linked dominant mode of inheritance for bipolar illness. Although one hallmark of an X-linked trait is reduced father-to-son-

transmission, this mode of transmission has, in fact, been reported several times (Goetzl et al. 1974, Gershon et al. 1975, James & Chapman 1975). Mendlewicz & Rainer (1974) reported X-linked transmission based on the assumption that the bipolar and unipolar relatives of bipolar probands were genotypically identical. The overall evidence for X-linkage remains doubtful, and an X-linked form of transmission may be present in some families (up to 25% of bipolar disorder, Baron et al. 1987). At least 3 genetic subtypes of bipolar illness exist, linked to genes on the X-chromosome, on chromosome 11 (Egeland et al. 1987), and probably at another, undetermined site.

One study (Gershon et al. 1975) has hypothesized that bipolar and unipolar illness are related according to the two-threshold model, with bipolar illness representing a more severe liability class. Gershon et al. (1982) recently extended this hypothesis to model schizo-affective, bipolar I, bipolar II and unipolar illnesses as separate liability classes on a single continuum and found their family data supportive of this multiple threshold paradigm. Angst et al. (1980) also found support for a simple two-threshold model for unipolar/bipolar illness but not for a more differentiated model in which bipolar illness is subtyped (according to unipolar mania and/or unipolar depression) in relation to reactivity.

Winokur & Clayton (1967) and Angst et al. (1980) suggest a sex difference in the transmission of illness, stating thereby that affected mothers transmitted their illness to significantly more daughters than sons, whereas affectively disordered fathers transmitted their illness equally to both sons and daughters. Using survival analysis, a maternal influence is found in primary major depression, with the mother having a greater effect on her offspring of either sex (Rice et al. 1984).

Psychosocial indications

Hudgens et al. (1967) were not able to substantiate the possible role of life events in the etiology of depression and mania, and in 1969, Paykel et al. concluded that life events, especially "exit" events, were implicated in the development of depression. Depressed patients had, in the months prior to the onset of illness, three times as many events as the control group. Brown et al. (1973) reported later that depressed women had experienced more life events in the three week period prior to the onset of illness than controls from the community. The relationship, however, betwen life events and mental health appeared to be weak, i.e., the contribution of life stress accounted for only about 10% of the variance in health (Rabkin & Struening 1976). Research has also revealed that personal characteristics, such as "lack of control" (Johnson & Sarasor 1978), "sensation-seeking" (Smith et al. 1978) and "hardiness" (commitment to the self – Kobasa 1979) were possible mediators in the relationship between life events, social support and health status. The role of the contextual significance in the experience of life events has been underlined by Brown & Harris (1978); they emphasised the contextual threat posed by life events as one of the etiological factors in depression. Paykel's "objective negative impact" was really a modification of Brown's "contextual threat".

One of the hazards of life events research in cases of depression concerns the diagnostic aspect. Firstly, the contamination of life event scales by the use of symptom-like items (i.e., change in eating habits) and, secondly, the actual diagnostics (Oei 1988). Age seems to play a secondary role in depression and mania diagnostics. Oei & Zwart (1988), for instance, were unable to confirm that age significantly influences the reporting of life events in (non)depressed patients. Cobb (1976) and Cassel (1976) hypothesized that social support can serve as an effective life stress

buffer. Indications of a relationship between lack of social support and the development and/or maintenance of disturbed behaviour, do exist however (Oei 1987). Before a real interaction between life events, social support and disturbed behaviour (i.e., depression and mania) can be analysed, careful specification and operationalisation of the concepts referred to, is called for (Oei & Zwart 1989).

Affective disorders and medical illness

The incidence of depressive disorders among medically ill patients varies in different studies from 5-50 % of all patients admitted to the General Hospital (Rodin & Voshart 1986). Those big differences in incidence do reflect the problem at its basis.

Depressive symptoms are confounded by somatic symptoms and vice versa. Fatigue, sleeplessness, loss of appetite, decrease of sexual desire and vaguely bodily complaints fit within the depressive syndrome as well as most internal diseases. Assessment of depressive symptoms by widely used questionnaires therefore becomes unreliable and is likely to show a much higher incidence of depression than by psychiatric interview (Hengeveld et al. 1988). Cavanough et al. (1983) tries to resolve this methodological problem by using the Beck Depression Inventory without the somatic items. This solution does not resolve the problems as underreport of depression may be the consequence.

The second problem one meets in studying the epidemiology of depression in the medically ill concerns the lack of strict distinctions between grief and depression. Grief is considered a psychologically healthy reaction to a serious threat like loosing one's health, vitality or life in the immediate future. Assessment of a patient's psychiatric status by questionnaire or by a structured psychiatric interview does not discriminate between these two states of mind. Nor is it clear when grief develops in time into a depression.

Depression in the medically ill is one of the most common affective disorders in the community. Many patients, however, do not develop a depression, even when confronted with a life-threatening disease. Mechanic (1962) was one of the first in his field to point out the striking differences between one patient and another, and emphasized the need to study not so much the question of failing adaptation, but rather what it is that enables some patients to maintain a degree of optimism whilst others apparently cannot. Medical psychological research may contribute to a better understanding of mood states in patients with acute and chronic diseases (Levine & Ursin 1980).

Illness is regarded as a life event and a stressor, both of which have to be coped with in order to restore the psychological and social equilibrium. The patient's coping ability is influenced by the severity and prognosis of the disease, his/her personality, his/her previous psychiatric history, cognitive impairment caused by the disease or its treatment, his/her relationship with the health care system, and the degree and quality of social support in his/her environment.

The result of this adaptation process influences both the patient's mood and the medical outcome (Mayou et al. 1988). Research into all these mutually-influencing factors, has only recently got under way, but preliminary findings (Levitan & Kornfeld 1981) suggest that the quality of the patient/medical-team relationship is of vital importance, as also the degree and quality of social support, for the intervention and prevention of inadequate adaptation to severe illness.

A high incidence of depression is found in patients facing drastic therapeutic regimes, such as long-term chemotherapy treatment and those with chronic and severely disabling diseases such as end-stage renal disease and rheumatoid arthritis (Smith et al. 1985). The treatment itself may also produce mood disorders, as in the case of high-dose prednisone therapy (Falk 1981).

The patient's personality, as such, and his previous psychiatric history, appear to be related more to his general reaction to the hospital system and the procedures that have to take place, than to the severity or chronicity of the disease itself. Special emphasis must be placed here on the role of cognitive impairment. Organic brain syndromes have a direct influence on the patient's mood and coping ability. Unlikely as it may seem to psychiatrists, their special symptoms are often missed on the wards (Trzepacz et al. 1985). The so-called "quiet delirium", in particular, may mimick a depression in the degree of its apparent apathy and social withdrawal and in patients with HIV infections, this is often one of the first signs of the Aids-dementia complex (Navia & Price 1987). The recognition and treatment of organic cognitive impairment has major implications for the patient's further treatment and prognosis.

Winokur et al. (1988) compared the severity and prognosis of secondary depression in the medically ill with the psychiatrically ill. It seems that the former tend to be more like the old neurotic depression and should respond better to treatment. Mayou et al. (1988) however, performed a longitudinal study with medically ill patients who suffered from depression. Their results indicate that depression is often badly recognised and treated and leads to a high medical consumption, poor medical outcome and impaired psychosocial functioning.

In conclusion, we would like to point out that research regarding the prevalence of depression among the medically ill is now widely available. The prognosis and treatment strategies however have hardly been studied. This seems all the more an important task for the future as depression influences costs of health care as well as medical outcome.

The bio-psychosocial model as an integration of the medical and psychosocial interpretations of affective disorders

In the 1970's, the study of multidisciplinary approaches in medicine in general and in psychiatry in particular, was based on the philosophy that every behavioural disorder comprises psychological, social and biological determinants (e.g., Van Praag 1972). Engel (1980) approached the problem from another angle and suggested a scientific (i.e., bio-psychosocial) psychiatric disease model, based primarily on the systems theory.

The rapidly growing body of knowledge in support of a link between a variety of psychic-distress and immuno-suppression states, constitutes a major step forward toward the establishment of a bio-psychosocial illness model.

Ehlers et al. (1988) have introduced a theoretical model for a "social zeitgeber theory". The most interesting aspect of this model is the integration of all the important (psychosocial and biological) components in the etiology of (depressive) behaviour. Intervening variables such as social support, coping, gender and personality can be influential factors in the chain of events in which social rhythm instability (air jet lag) can lead to disturbances in one or more of the biological rhythms, such as sleep. This instability might also lead to somatic symptoms and function as protective and vulnerability factors of both a psychosocial and a biological nature. The depression serves then, in vulnerable individuals, as the final psycho-biological response to negative changes in the social rhythms. If further research were to clarify the authenticity of such a model, it might also provide an explanation for the etiology and phenomenology of psychiatric (i.e., depressive) disorders.

For the moment, we can perhaps accept that in affective disorders the interaction between psyche, soma and environment has been shown to be the most coherent of all the existing models used for the ex-

planation of psychiatric syndromes (e.g., Gold et al. 1988).

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